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Review

Circadian rhythms and rheumatoid arthritis

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ABSTRACT

Circadian rhythms (Nobel prize for Medicine 2017) regulate, under action of biological clocks located both at the level of central nervous system and inside peripheral cells, several daily activities, embracing sleep, feeding times, energy metabolism, endocrine and immune functions with related pathological conditions, including rheumatoid arthritis (RA).

In RA the circadian rhythms impact on cellular functions, involving night synthesis and release of pro-inflammatory cytokines and chemokines, cell migration to inflamed tissues, phagocytosis, proliferative cell response and all are peaking at late night. In chronic inflammatory conditions such as RA, the amplitude of the circadian rhythm of the anti-inflammatory endogenous cortisol availability is not increased as expected and requested, which indicate a reduced night cortisol secretion under the adrenal chronic stress induced by the disease. Therefore, the prevention/treatment of the immune cell night hyperactivity, with related flare of cytokine synthesis and morning RA clinical symptoms, has been shown more effective when the availability of the exogenous glucocorticoids is obtained in the middle of the night (night release). The impressive positive results observed in RA patients treated with modified-night release prednisone with a low-dose chronotherapy, seem applicable even for other agents such as conventional NSAIDs and DMARDs, including the positive experimental and clinical results obtained by the night time daily administration of methotrexate. Interestingly, a very recent study showed that methotrexate upregulates important cell circadian genes, resulting in induction of apoptosis in synovial fibroblasts. The link between the circadian rhythms of the disease and the chronotherapy of RA is promising.

1. Introduction

The Nobel Prize for Physiology or Medicine has been conferred in 2017 to scientists who contributed to the discovery of the network of genes and proteins regulating the peripheral circadian rhythms based on the light/dark 24-hour cycle [1,2] (Fig. 1).

In humans, circadian rhythms are synchronized to coincide with the daily rotational cycle of the earth. An intricate system of intermolecular interaction modulates the 24-hour rhythms in cells and this cycle is normally maintained and readjusted by both central and peripheral mechanisms.

More in detail, circadian rhythms originate from a central pacemaker in the suprachiasmatic nucleus (SCN) in the brain, photoentrained via direct connection with melanopsin containing, intrinsically light-sensitive retinal ganglion cells, and it projects to periphery by creating along this process an inner circadian rhythm [3] (Fig. 1).

Possible causes of disruption of the circadian clock should include jet lag, causing a desynchrony between the internal clock and the environment (light-darkness), as well as the condition of night shift-workers [4,5].

The circadian rhythms regulate several activities, including sleep, feeding times, energy metabolism, and of crucial importance the endocrine and immune functions. Disturbances of these rhythms, mainly of wake/sleep, hormonal secretion and feeding, are involved in development of obesity, metabolic syndrome as well as allergic and immunological diseases, including bronchial asthma and rheumatoid arthritis (RA). A very recent project/study will identify sleep/wake rhythm-associated parameters that predict health-related quality of life (HRQoL) in patients with RA [6–9].

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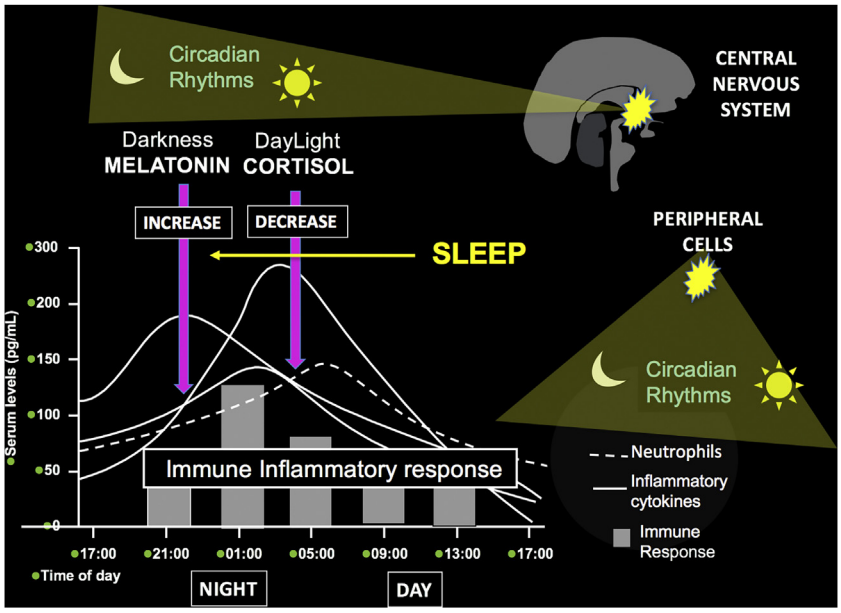

Fig. 1. The circadian rhythms originate from both the central nervous system and from inside the peripheral cells, based on the light/dark 24-hour cycle. Melatonin (released with darkness) and cortisol (released with light) up- and down-regulate, respectively, the immune-inflammatory response during the night (sleep). Consequently, a large range of immune response mediators, such as the peripheral blood mononuclear cells, as well as the concentrations of cytokines, undergo daily fluctuations.

2. Circadian rhythms and the immune function

A large range of immune response mediators, such as the peripheral blood mononuclear cells, as well as the concentrations of cytokines, undergo daily fluctuations [10].

In addition, the total numbers of hematopoietic stem cells and several mature leukocytes peak in the circulation during the night and decrease during the day [6].

Most immune cells express circadian clock genes and present a wide array of genes expressed with a 24-hour rhythm [11].

This rhythm has weighty impacts on cellular functions, including night synthesis and release of cytokines and chemokines, as well as through pattern recognition receptors, regulates circadian immune system functions such as cell migration to inflamed or infected tissues, phagocytosis, cytolytic activity, and proliferative response to pathogenic antigens, all peaking (or start picking) at late night [12,13] (Fig. 1).

On the other hands, recent studies have helped to elucidate the influence of inflammatory cytokines on circadian mechanisms. Interestingly, activation of the immune system counteracts infection and increases resistance to pathogens by inducing slow wave sleep, presumably via the production of inflammatory cytokines such as TNF-α, IL-2, or IFN-gamma that are known to induce slow wave sleep [14].

Lipopolysaccharide (LPS), which is the major component of the outer membrane of Gram-negative bacteria, increases the secretion of these cytokines. LPS-dependent secretion of TNF-α is significantly higher at night compared to day and is further enhanced by the night hormone melatonin [15].

Very recently TNF-α has been found to induce expression of the circadian clock gene *Bmal1* via dual calcium-dependent pathways in rheumatoid synovial cells, further supporting influence of immune-inflammatory response mediators on circadian mechanisms [16].

Therefore, another study demonstrated an active molecular clock within the inflamed joint in a mouse model of arthritis and highlighted that resident inflammatory cells such as the fibroblast-like synoviocytes (FLSs), are a potential local further source of the rhythmic inflammatory signal [17].

3. Neuroendocrine circadian control on the immune-inflammatory response

One of the mechanisms through which the central clock entrains peripheral tissues is by the production of glucocorticoids by the adrenal gland [18].

However, many other circadian signal transduction mediators also regulate the immune response, as the night neurohormone melatonin and the autonomic nervous system.

Therefore, the central nervous system synchronizes peripheral clocks via mediators including hormones and neuronal signals, primarily using the hypothalamic – pituitary – adrenal (HPA) axis and the autonomic nervous system [19].

The principal hormones i.e. glucocorticoids and catecholamines (epinephrine and norepinephrine), are released by the adrenal gland via the HPA axis [29], but norepinephrine is also derived from the sympathetic nerve endings [20].

The HPA is controlled by the SCN which projects to the paraventricular nucleus of the hypothalamus, and this in turn induces the release of adrenocorticotropic hormone by the pituitary, in this manner regulating the adrenal gland [21,22] (Fig. 1).

Catecholamines act via adrenergic receptors, which have many effects on immune cells, as well as increasing the humoral immune responses [6].

In the daytime, light-initiated signals are transmitted via the SCN to the pineal gland through the upper cervical ganglion. Melatonin, as mentioned is the neurohormone that mediates circadian rhythm adjustment and is produced by the pineal gland at night [23] (Fig. 1).

Therefore, light stimulus causes an increase in the secretion of cortisol, serotonin, and dopamine, while suppressing melatonin, norepinephrine, and acetylcholine. Serum melatonin concentrations are normally undetectable in the daytime but are significantly higher during the night, in the absence of light optical stimulation [24].

As compared with healthy subjects, melatonin secretion at midnight is significantly increased in patients with chronic inflammation like in RA and melatonin serum levels in the early morning are higher in RA patients with shorter disease duration [25,26].

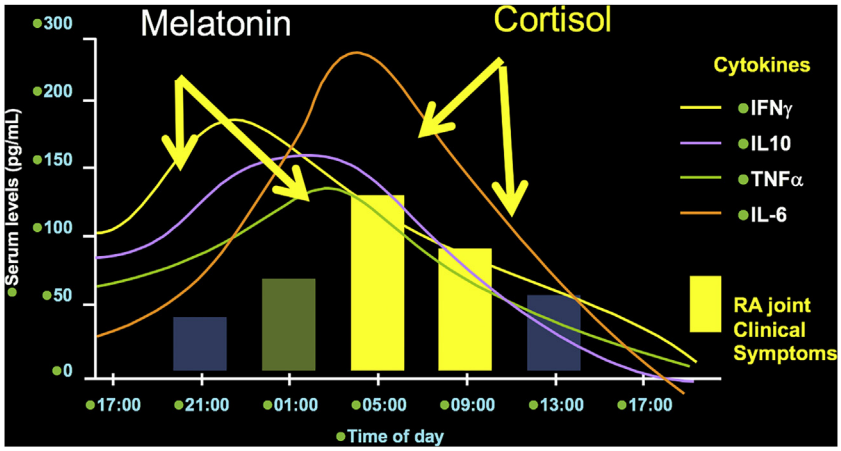

Fig. 2. The pattern of cytokine release and their serum concentrations, triggered by pro-inflammatory hormones such as hormones melatonin (and prolactin), follow a strict 24-hour daily cycle. Therefore, these pro-inflammatory start to rise before the onset of RA symptoms and before that the circadian endogenous cortisol synthesis will be activated in order to counteract the cascade of the inflammatory disease mediators (and related joint symptoms).

Inflammatory cytokines including IFN-gamma, IL-1, and IL-6 are all secreted during the night from human peripheral blood mononuclear cells in response to melatonin stimulation, and in fact, melatonin (and its receptors) are detected in both normal and RA synovial tissue macrophages and fluid [15] (Fig. 1).

Recently, melatonin has been shown to stimulate cartilage destruction/regeneration through direct/indirect modulation of the expression of the main circadian clock genes, such as BMAL, CRY and/or DEC2 [27].

4. Coupling circadian rhythms of cytokine production and bioenergies distribution with clinical symptoms in rheumatoid arthritis

The clinical consequence of the night elevated synovial levels of pro-inflammatory cytokines is the presence of circadian clinical joint symptoms of RA, such as morning joint stiffness and pain, as now generally accepted [28–30].

As mentioned, the pattern of cytokine release and their serum concentrations, triggered by pro-inflammatory hormones such as melatonin (and prolactin), follow a strict 24-hour daily cycle. Therefore, these pro-inflammatory hormones start to rise before the onset of RA symptoms and before that the circadian endogenous cortisol synthesis will be activated in order to counteract the cascade of the inflammatory disease mediators and symptoms [31] (Fig. 2).

It should be also considered that rhythmic fluctuations of the nocturnal secretion and the peripheral metabolism of endogenous cortisol, as well as changes in the activation in the synovial cells of biologically inactive to active cortisone, may play a role in the pathophysiology of RA [31].

In RA patients, the whole inflammatory process induces changes in synovial fluid composition, edema of the synovial tissue and periarticular structures, as well as redistribution of interstitial fluid, whereas sleeping with different mechanisms, contributes to the clinical stiffness of the joints that is most pronounced in the morning.

Among several important circadian players, energy distribution is important for homeostatic regulation of physiological processes and is daily allocated according to the different metabolic activities during the 24-hour cycle [32] (Fig. 3).

Neuroendocrine pathways are patterns in energy distribution and are grouped as factors that provide energy-rich fuels to stores (i.e. parasympathetic nervous system, insulin, insulin-like growth factor-1) and those that provide energy-rich substrates to consumers/reactors [i.e. sympathetic nervous system (SNS), HPA axis, thyroid hormones, glucagon and growth hormone] [33,34].

In normal conditions the allocation of energy-rich fuel to stores and users is balanced, is distributed according to circadian rhythms and linked to energy-consuming daily physiological activities (i.e. during the day for muscle and cardiovascular function). However, in chronic inflammatory conditions such as active RA, this balance is altered due to the large energy use by the nocturnal hyperactivation of the immune system [34] (Fig. 3).

As anticipated, during sleep, the increased energy need for the immune system functions, including cell proliferation, can much more easily be available due to the dramatic reduction of all the other energy-consuming activities (i.e.muscle and cardiovascular functions) [34] (Fig. 3).

Nevertheless, energy regulation is inadequate in chronic inflammatory conditions and induces many other clinical abnormalities, including cachexia, anorexia, sickness behaviour, dyslipidaemia, fat deposits near inflamed tissue, insulin resistance and hyperinsulinaemia, activation of the SNS (hypertension), mild hypercortisolaemia, hypoandrogenaemia as well as chronic inflammation related anemia and osteopenia [35]. Interestingly, many of these conditions can be involved in causing the metabolic syndrome.

Generally, constant shifts in the daily schedule are detrimental to health and have been linked with an increased incidence of a number of chronic diseases such as cardiovascular disease, irritable bowel syndrome, metabolic syndromes, diabetes, cancer and a study in 2010 provided a significant link also with the increased risk of RA [5,36].

In conclusion, circadian signs and joint symptoms of RA arise also in the context of a larger availability during the night of energy-rich fuels for the increased immune system activation [35].

5. Altered circadian production of cortisol in rheumatoid arthritis

In presence of acute pro-inflammatory events, such as bacterial infections, the HPA axis response is activated and leads to high concentrations of circulating ACTH and cortisol. In particular, daily production of cortisol can increase by a factor of 18 in severe conditions like the first days of sepsis [37].

However, this strong adrenal stimulation only lasts for a short period of time like a few days. Conversely, inflammation-associated activation of the HPA axis activity in presence of chronic inflammation, such as in RA, can harm the HPA axis on all levels

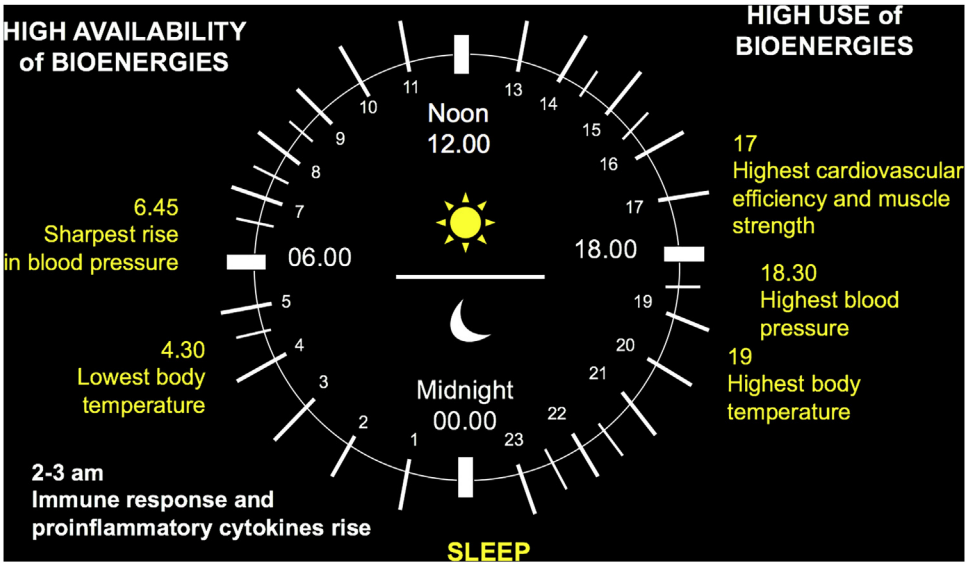

Fig. 3. Among several important circadian players, energy distribution is important for homeostatic regulation of physiological processes and is daily allocated according to the different metabolic activities during the 24-hour cycle. In normal conditions the allocation of energy-rich fuel to stores and users is balanced, is distributed according to circadian rhythms and linked to high use of bioenergies for daily physiological activities (i.e. during the day for muscle and cardiovascular function). However, in chronic inflammatory conditions such as active RA, this balance is altered due to the large energy use by the nocturnal hyperactivation of the immune system.

(hypothalamus, pituitary gland and adrenal gland) and can lead to a partial adrenal insufficiency [38].

The pro-inflammatory cytokines IL-1β and TNF are the main factors which interfere with several steps of steroidogenesis [39].

However, the circadian rhythm of serum cortisol with respect to amplitude and period is similar in healthy controls and in RA patients affected by mild to moderate disease. In contrast, serum concentrations of IL-6 are almost 10 times higher and the circadian rhythm is quite different in controls and in RA patients. Therefore, despite raised serum concentrations of IL-6, the amplitude of the circadian rhythm of cortisol is not increased as expected and requested, which is indicative of inadequate cortisol secretion under adrenal chronic stress related to constant active disease [38] (Fig. 3).

The clinical improvement observed after glucocorticoid therapy in patients with RA appeared in previous studies should be attributed to a direct dampening of pro-inflammatory factors, as well as to the restoration of the steroid milieu [40].

In conclusion, since cortisol is the strongest endogenous anti-inflammatory hormone, its abnormal hyposecretion during the night in chronic diseases, may justify the presence of the early morning clinical joint symptoms in patients with RA, while in contrast the synthesis of melatonin is still high and enhances the night inflammatory reaction [40].

6. Chronotherapy and glucocorticoids in rheumatoid arthritis

Low-dose long term glucocorticoid treatment is today recommended in RA since it may act as a 'replacement therapy' in the presence of decreased endogenous cortisol adrenal production [41,42].

In reality, exogenous glucocorticoids (i.e., therapeutic) and endogenous glucocorticoids (i.e., physiological) show different characteristics.

Exogenous synthetic glucocorticoids exhibit a more selective glucocorticoid/ anti-inflammatory action (less mineralocorticoid effects), as well as have a different plasma kinetics, biological half-life, metabolism and non-genomic high-dose effects compared to cortisol (hydrocortisone).

In any case, long-term exogenous glucocorticoid administration may interfere with the HPA axis function and with the circadian cortisol adrenal production.

Interestingly, a reduction of mean initial low-dose from 10.3 to 3.6 mg/day (prednisone) in presence of long-term RA glucocorticoid therapy has been observed in one recent analysis during the period 1980–2004 and indicate a better approach to the correct long term use of glucocorticoids [43].

Recently, it became evident that glucocorticoids exert important genomic-epigenetic effects on cellular immunity and, given the presence of cellular circadian rhythms, therefore the prevention of the night upregulation of immune cell activity (and related increase of cytokine synthesis and cell proliferation) with their exogenous administration between 6:00 and 8:00 may not be optimal, since it is too late to interfere with the activation of the nocturnal inflammatory/proliferative processes [44,45] (Fig. 4).

Since it has been established that RA pain, stiffness and functional disability show maximum levels in the early morning, it is now clear that preventing the nocturnal rise of pro-inflammatory cytokines by glucocorticoid availability in the night, is more effective than treating established symptoms in the morning [23,39] (Fig. 4).

Furthermore, a number of inflammatory pathways also implying the central nervous system in RA (i.e., pain perception) and in polymyalgia rheumatica might be better controlled by the glucocorticoid chronotherapy, resulting in increased sleep quality and reduction of related depressive symptoms [46,47]. Aging may even increase the need for a more careful management of glucocorticoids [48].

The first reliable clinical study showing the superiority of night versus morning administration of glucocorticoids in RA was published in 1964 [49].

Twenty years later, in 1984, 41 patients with RA treated with low-dose prednisolone (mean 5.8 mg/day) participated in a double-blind crossover study to again determine the effect of timing (morning or night) of prednisolone dosage on morning stiffness [50]. Two different regimens were adopted; tablets (< 5 mg/day prednisolone) on retiring (22:00–23:00) or on rising (6:00–7:00). Again prednisolone given at night resulted in a significantly shorter

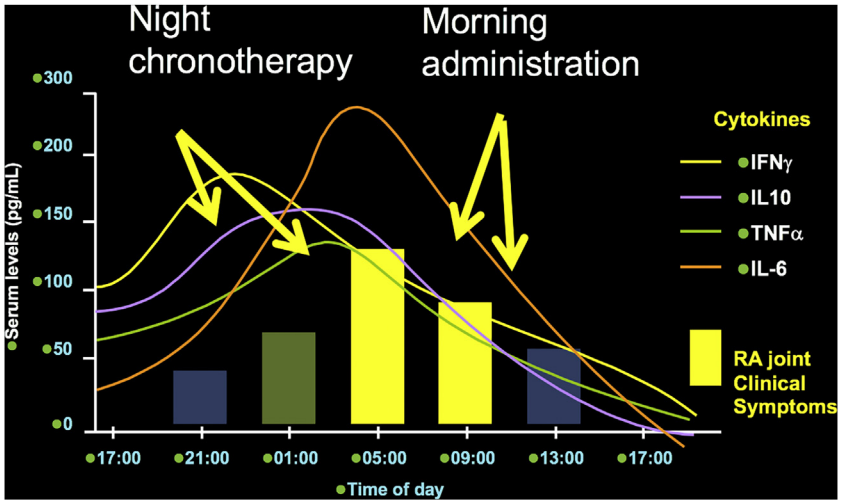

Fig. 4. The prevention of the night upregulation of immune cell activity (and related increase of cytokine synthesis and cell proliferation) with the exogenous morning administration of glucocorticoids between 6:00 and 8:00, may not be optimal, since it is too late to interfere with the activation of the nocturnal inflammatory/proliferative processes. Since it has been established that RA pain, stiffness and functional disability show maximum levels in the early morning, it is now clear that preventing the nocturnal rise of pro-inflammatory cytokines by exogenous glucocorticoid availability in the night, is more effective than treating established symptoms in the morning.

duration of morning stiffness ($P = 0.0001$) than did an equivalent dose given in the morning.

Finally, in 1997, 26 glucocorticoid-untreated RA patients were randomly divided into two equal groups and treated with low-doses of prednisolone at either 2.00 am or 7.30 am [51].

Administration of low-doses of prednisolone (5 or 7.5 mg daily) at 2:00 am, after only 5 days, showed very favourable effects on the duration of morning stiffness ($P < 0.001$), joint pain ($P < 0.001$), Lansbury index ($P < 0.001$), Ritchie index ($P < 0.001$) and morning serum concentrations of IL-6 ($P < 0.01$). The other study group (7.30 am) showed minor but significant effects whereas limited to morning stiffness ($P < 0.05$) and circulating concentrations of IL-6 ($P < 0.05$). This further investigation confirmed that administration of low-doses of glucocorticoids seems to improve acute RA symptoms if it precedes (night) the period of circadian flare in inflammatory activity, as defined by enhanced IL-6 synthesis.

More recently, the most advanced approach for the low-dose prednisone chronotherapy in RA included the modified-release prednisone, a timing drug release with administration at 22:00, and releasing prednisone around 2:00– 3:00 versus morning immediated-release (CAPRA study, Circadian Administration of Prednisone in Rheumatoid Arthritis) [52,53].

The mean relative change in duration of morning joint stiffness from baseline to end was found significantly higher with modified-release prednisone than with immediate-release prednisone ($P = 0.045$). The absolute difference between the treatment groups was 29.2 min (95% CI – 2.59 to 61.9) in favour of modified-release prednisone ($P = 0.072$).

Interestingly the incidence of severe adverse events during the first 3 months (morning administration) of treatment was 2.4% compared with only 3.3% in patients receiving 12 months of night release prednisone administration (4 time longer period) [53].

7. Other approaches to chronotherapy in rheumatoid arthritis

Different cells involved in the inflammatory process (i.e. monocytes that lose their normal circadian rhythms during the inflammatory conditions) are particularly activated during the night, therefore, other therapeutical approaches used in RA, for example non- steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and aceclofenac, have been synthesized in order to follow the same concepts of glucocorticoid chronotherapy [54–56] (Fig. 1).

As a matter of fact, the circadian activation of the cells involved in the RA immune/inflammatory response represents the preferential target for conventional and biologic DMARDs, therefore, also the administration of anti-proliferative drugs (i.e., methotrexate, leflunomide, cyclophosphamide, etc.) should consider those rhythms (Fig. 4).

This hypothesis was tested in an in vivo investigation using an animal model of arthritis, and showed that the optimal dosing time, associated with the 24-hour cycling of TNF-α, could result in the most efficient methotrexate anti-inflammatory activity and the most effective decrease of TNF-α [57]. A further clinical study has confirmed that chronotherapy with methotrexate at bedtime (3 times a week once a day in the evening) can further improve RA symptoms compared to the current standard dosing methods [58].

A more recent investigation, looking at the plasma IL-6 levels in collagen-induced arthritis (CIA) rats, showed that the daily administration of MTX after 6 weeks, was more potent than weekly administration based on a more significant reduction of the IL-6 circadian rhythm, as well the arthritis score and TNF-α and CRP levels [59].

Interestingly, a very recent study showed a novel unique circadian mode of action of methotrexate on synovial fibroblasts, that upregulates the circadian transcriptional factor proline and acidic amino acid-rich basic leucine zipper (PAR bZIP) and the circadian clock gene *PERIOD2* (*PER2*) resulting in apoptosis induction [60]. Therefore, methotrexate seems important in modulating circadian environments and to understand new aspects of RA pathogenesis.

8. Conclusions

The early morning clinical joint symptoms that characterize RA patients, are related to the circadian night activation of the immune/inflammatory response. The prevention/treatment of the immune cell activity (and related flare of cytokine synthesis and other mediators) has been shown more effective when the availability of the exogenous glucocorticoids is obtained in the middle of the night. The impressive positive results observed in RA patients treated with modified-night release prednisone with a low-dose chronotherapy, seem applicable even for other therapeutical agents.

Since it has been established that RA pain, stiffness and functional disability show maximum levels in the early morning, it is now clear that preventing the nocturnal rise of pro-inflammatory cytokines by glucocorticoid administration in the night, is more effective than treating established symptoms in the morning including conventional NSAIDs and DMARDs, such as the encouraging results obtained by the night time daily administration of methotrexate.

We consider that in order to achieve the best results, at least in RA treatment, the concept of chronobiology/therapy should be introduced as soon as possible in guidelines for conducting RA new drug registration trials.

Disclosure of interest

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